Remarks

Claims 1-3 are pending. Claim 5 has been cancelled. Claim 8 has been added. Claim 1 was amended to define the CatK inhibitor as N-[1-(cyanomethyl-carbamoyl)-cyclohexyl]-4-[4-(1-propyl)-piperazin-1-yl]-benzamide. Support for this amendment can be found throughout the specification and Examples. Claim 2 was amended to define the pharmaceutical preparation according to claim 1 for the treatment of bone metastasis and cancer therapy-induced bone loss. New claim 8 defines the pharmacologically acceptable salt of N-[1-(cyanomethyl-carbamoyl)-cyclohexyl]-4-[4-(1-propyl)-piperazin-1-yl]-benzamide as the hydrogen maleate. Support for this new claim can be found throughout the specification. More specifically, third full paragraph on page 18 of the specification.

The first full paragraph on page 4 of the specification has been amended to define the term "treatment" as including treatment of patients suspected to have contracted the disease as well as ill patients. The terms preventative and prophylaxis have been deleted.

35 U.S.C. 112, first paragraph rejection

Claims 1-3 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of bone metastasis, does not reasonably provide enablement for the prevention or prophylaxis of bone metastasis.

Claim 1 defines a pharmaceutical preparation and does not define a method of treatment. Therefore, it should not be rejected under 35 U.S.C. 112, first paragraph and Applicants respectfully request the rejection against claim 1 be withdrawn.

In response to the Examiner's rejection, the definition of treatment has been amended to define the terms as treatment of patients suspected to have contracted the disease as well as ill patients, please refer to the first paragraph on page 4 of the specification. Applicants believe claims 2 and 3 satisfy the requirements of 35 U.S.C. 112, first paragraph.

35 U.S.C. 103(a) Rejection

Claims 1-3 and 5 were rejected under 35 U.S.C. 103(a) as being unpatentable over Okuno et al (US 2002/0142996) in view of Altman et al (WO 03/020278). The Examiner argues that it is obvious to combine two compositions each of which is taught by the prior art to be useful in the treatment of tumor metastasis. Therefore, the Examiner argues it would have been obvious to one of ordinary skill in the art at the time of the instant application to combine zoledronic acid and N-[1-(cyanomethyl-carbamoyl)-cyclohexyl]-4-[4-(1-propyl)-piperazin-1-yl]-benzamide into a single composition and to administer said composition to a patient to treat bone metastasis. Applicants respectfully disagree.

US 2002/0142996 and WO 03/020278 do not teach or suggest combining these two combination agents for the treatment of cancer.

The present invention relates to the combinations of zoledronic acid and N-[1-(cyanomethyl-carbamoyl)-cyclohexyl]-4-[4-(1-propyl)-piperazin-1-yl]-benzamide or a pharmaceutically acceptable salt thereof for the treatment of various diseases. Example 2 on page 27 of corresponding WO 2005/014006 describes combining zoledronic acid with N-[1-(cyanomethyl-carbamoyl)-cyclohexyl]-4-[4-(1-propyl)-piperazin-1-yl]-benzamide or its hydrogen maleate salt to treat cell lines with osteolytic activity. The results of the experiment state that the combination is expected to exhibit an additive anti-osteolytic activity which is superior to single treatment. Example 3 on page 29 of the specification describes combining zoledronic acid with N-[1-(cyanomethyl-carbamoyl)-cyclohexyl]-4-[4-(1-propyl)-piperazin-1-yl]-benzamide or its hydrogen maleate salt to treat bone metastasis. None of the cited prior art teaches or suggests the combination of zoledronic acid with N-[1-(cyanomethyl-carbamoyl)-cyclohexyl]-4-[4-(1-propyl)-piperazin-1-yl]-benzamide or its hydrogen maleate salt and Applicants argue that the present claims are nonobvious over the cited prior art.

US2002/0142996A1 describes methods of treating angiogenesis comprising administering a bisphosphonates, specifically zoledronic acid. Angiogenesis is the formulation of new blood cells from pre-existing blood cells. US2002/0142996A1 does not teach or suggest using zoledronic acid as described in the Examples of the present application. WO2003/020278 describes a number of CatK inhibitors with a genus chemical structure. Numerous compounds are described and the reference does not suggest that N-[1-(cyanomethyl-carbamoyl)-cyclohexyl]-4-[4-(1-propyl)-piperazin-1-yl]-benzamide or its hydrogen maleate salt would be a good combination agent for the treatment of bone disease. The Examples of WO2003/020278 describe processes for making the CatK inhibitors. There are no working Examples describing the therapeutic benefits of the CatK inhibitors for the treatment of bone metastasis or osteolytic activity. A person would not look to the teachings of WO2003/020278 to arrive at the claimed therapeutic combination. It would not have been obvious, based on the teachings in these two references, to combine the compounds for the therapeutic treatment described in the Examples.

Entry of this Response is respectfully requested.

Respectfully submitted,

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